CLAIMS

1. A method of culture of embryonic stem (ES) cells, comprising maintaining the ES cells in the presence of a compound which selectively promotes self-renewal of the ES cells and/or inhibits propagation or survival of cells other than ES cells.

2. A method according to Claim 1 wherein the compound inhibits a cell signalling pathway and wherein maintenance or activation of the pathway is essential to propagation or survival of cells other than ES cells but is not essential to propagation or survival of ES cells.

3. A method according to Claim 1 or 2, wherein the compound inhibits cyclin dependent entry into S-phase of cells other than ES cells.

4. A method according to Claim 1, 2 or 3 wherein the compound inhibits or reduces the activity of the enzyme SHP-2.

5. A method according to any of Claims 1 to 3 wherein the compound inhibits or reduces the activity of the ras/MAPK cascade.

6. A method according to any of Claims 1 to 3 wherein the compound inhibits or reduces the activity of MEK.

7. A method according to any of Claims 1 to 3 wherein the compound inhibits or reduces the activity of a mitogen activated protein kinase.

8. A method according to any of Claims 1 to 3 comprising using a combination of at least two compounds selected from compounds that inhibit SHP-2, the ras/MAPK cascade, MEK and a mitogen activated protein kinase.

9. A method of culture of ES cells comprising maintaining ES cells in

the presence of a first compound that promotes proliferation of ES cells and a second compound that enhances the response of the cells to the first compound.

10. A method according to Claim 9, wherein the first compound acts through a cell-surface receptor and exerts its activity through at least one receptor subunit, and the second compound modifies an intracellular signalling pathway so as to increase the response of the ES cell to the first compound.

11. A method according to Claim 9 or 10, wherein the second compound is an inhibitor of the ras/MAPK cascade.

12. A method of culture of ES cells comprising maintaining a culture of ES cells in the presence of:-

(a) a compound that promotes propagation or survival of ES cells; and

(b) a compound that inhibits propagation or survival of cells other than ES cells.

13. A method according to Claim 12, wherein the combination of compounds (a) and (b) is synergistic.

14. A method according to Claim 12 or 13 wherein compound (b) selectively inhibits a signalling pathway essential to propagation or survival of cells other than ES cells.

15. A method according to any of Claims 12 to 14, wherein compound (b) is selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated

protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

16. A method according to any of Claims 12 to 15 wherein compound (a) is a cytokine that activates the cytokine receptor gp130 in ES cells.

17. A method according to Claim 16, wherein the cytokine is LIF.

18. A composition for selective culture of ES cells, comprising (a) a compound that inhibits differentiation of ES cells, and (b) a synergistic amount of a compound that inhibits propagation or survival of cells other than ES cells.

19. A composition according to Claim 18 wherein compound (b) selectively inhibits a signalling pathway essential to propagation or survival of cells other than ES cells.

20. A composition according to Claim 18 or 19 wherein compound (b) is selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

21. A composition according to any of Claims 18 to 20 wherein compounds (a) is a cytokine that binds to the cytokine receptor gp130, such as LIF.

22. Use of a compound that selectively inhibits propagation or survival of cells other than ES cells in a method of obtaining a substantially pure culture of ES cells.

23. A culture medium for culture of ES cells and comprising a compound

that selectively inhibits propagation or survival of cells other than ES cells.

24. A culture medium according to Claim 23, comprising a compound selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

25. A culture medium for culture of ES cells and comprising a first compound that promotes proliferation of ES cells and a second compound that enhances the response of the ES cells to the first compound.

26. A culture medium according to Claim 25, wherein the first compound acts through a cell-surface receptor and exerts its activity through at least one receptor subunit, and the second compound modifies an intracellular signalling pathway so as to increase the response of the ES cell to the first compound.

27. A culture medium according to Claim 25 or 26 wherein the second compound is selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

28. A culture medium for culture of ES cells and comprising (a) a compound that promotes proliferation of ES cells, and (b) a compound that inhibits propagation or survival of cells other than ES cells.

29. A culture medium according to Claim 25, wherein the combination of compounds (a) and (b) is synergistic.

30. A culture medium according to Claim 28 or 29, wherein compound

(b) selectively inhibits a signalling pathway essential to propagation of cells other than ES cells.

SUB A4 CONT.

31. A culture medium according to any of Claims 28 to 30, wherein compound (b) is selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

32. A culture medium according to any of Claims 28 to 31, wherein compound (a) is a cytokine that activates the cytokine receptor gp130 in ES cells.

33. A culture medium according to Claim 32, wherein the cytokine is LIF.

34. A method of deriving ES cells comprising isolating cells from an embryo or embryoid body and maintaining a culture of those cells in the presence of a compound that selectively inhibits propagation or survival of cells other than ES cells.

35. A method according to Claim 34 comprising dissociating cells obtained and then further maintaining the dissociated cells in the presence of the or a further compound that selectively inhibits propagation or survival of cells other than ES cells.

SUB A5

36. A method according to Claim 34 or 35 comprising developing an embryo *in vivo*, harvesting the embryo prior to pro-amniotic cavity formation and isolating cells therefrom.

37. A method of deriving ES cells comprising developing an embryo *in vitro*, isolating cells from the inner cell mass of the embryo and maintaining those cells in the presence of a compound that selectively inhibits

propagation or survival of cells other than ES cells.

38. A method according to Claim 37 comprising removing primitive endoderm prior to culture in the presence of the compound.

SUB A6

39. A method according to any of Claims 34 to 38, wherein the compound that selectively inhibits propagation or survival of cells other than ES cells is selected from compounds which inhibit activity of the enzyme SHP-2, inhibit the ras/MAPK cascade, inhibit MEK, inhibit a mitogen activated protein kinase or inhibit cyclin dependent entry into S-phase of non-ES cells.

40. A method according to any of Claims 1 to 8, comprising maintaining the ES cells in the presence of a compound which selectively promotes self-renewal of the ES cells.

41. A method according to any of Claim 1 to 8, comprising maintaining the ES cells in the presence of a compound which selectively inhibits propagation or survival of cells other than ES cells.

42. A method according to any of Claims 1 to 8, comprising maintaining the ES cells in the presence of a MAP kinase phosphatase.

SUB A7

43. A method of culture of ES cells, comprising expressing in the ES cells a compound which selectively promotes self-renewal of the ES cells and/or inhibits propagation or survival of cells other than ES cells.

44. A method according to Claim 43, comprising expressing a MAP kinase phosphatase in an ES cell.

45. Use of a compound that selectively promotes self renewal of ES cells in a method of obtaining a substantially pure culture of ES cells.

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